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(71) Applicant *(for all designated States except US)*: **PHARMACIA & UPJOHN SPA** [IT/IT]; Via Robert Koch, 1.2, I-20152 Milan (IT).

(71) Applicants and
(72) Inventors: **TOMASI, Attilio** [IT/IT]; Via Tommaso Gulli, 49, I-20147 Milan (IT). **MAGENES, Stefania** [IT/IT]; Via Oreglio, 8, I-20066 Melzo (IT). **UNGARI, Mario** [IT/IT]; Via Pietro Calvi, 10, I-20129 Milan (IT). **RAMELLA, Giuliano** [IT/IT]; P.le Europa, 1A, I-26019 Vailate (IT). **PALLANZA, Gianfranco** [IT/IT]; Via Savona, 94/A, I-20144 Milan (IT).

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WO 01/70740 A1

(54) Title: PROCESS FOR PREPARING CRYSTALLINE FORM I OF CABERGOLINE

(57) Abstract: A process for producing crystalline form I of cabergoline, which process comprises crystallization of the desired form from a toluene/diethyl ether mixture comprising raw cabergoline, followed by recovery and drying of the resulting crystals. A new solvate form V of cabergoline, useful as an intermediate, is also provided.

Process for preparing crystalline form I of cabergoline

The present invention concerns a new process for preparing crystalline Form I of cabergoline.

Cabergoline is an ergoline derivative interacting with D2 dopamine receptors and is endowed with different useful pharmaceutical activities and it is used in the treatment of hyperprolactinemia, central nervous system disorders (CNS) and other related diseases.

Cabergoline is the generic name of 1((6-allylergolin-8beta-yl)-carbonyl)-1-(3-dimethylaminopropyl)-3-ethylurea, described and claimed in US 4,526,892. The synthesis of cabergoline molecule is reported also in Eur. J. Med. Chem., 24,421,(1989) and in GB-2,103,603-B. Crystalline cabergoline Form I, an anhydrous not solvated form of cabergoline, was prepared by crystallization from diethyl ether, as described in Il Farmaco, **50** (3), 175-178 (1995).

Cabergoline Form I, like cabergoline, displays a significant inhibitory effect with regard prolactine and has therapeutic properties that make it possible to treat patients who have pathological conditions associated with an abnormal prolactin level, thus is useful in human and/or veterinary medicine. Cabergoline is also active, alone or in combination, in the treatment of reversible obstructive airways diseases, for controlling intraocular pressure and for the treament of glaucoma. It is also employed in the veterinary field, as antiprolactin agent and in cutting down drastically the proliferation of vertebrate animals. The several uses of cabergoline are for example described in WO9948484, WO9936095, US5705510, WO9505176, EP040,325. Cabergoline Form I is particularly useful in the treatment of Parkinson's disease (PD), Restless Legs Syndrome (RLS), treatment of diseases like Progressive Supranuclear Palsy (PSP) and Multysystemic atrophy (MSA).

During our development work we discovered a new process for preparing crystalline Form I.

Thus, the present invention concerns a new process for preparing Form I of cabergoline and a new solvate Form V of cabergoline useful as intermediate.

Description of figures

Figure 1. XRD powder pattern of cabergoline Form I.

Figure 2. DSC curve of cabergoline Form I.

Figure 3. IR spectrum of cabergoline Form I (sample prepared by KBr powder technique).

Figure 4. Solid state ^{13}C-NMR spectrum of cabergoline form I.

Figure 5. XRD powder pattern of cabergoline solvate Form V.

Figure 6. DSC curve of cabergoline solvate Form V.

Figure 7. IR spectrum of cabergoline solvate Form V (sample prepared by KBr powder technique).

Figure 8. Solid state ^{13}C-NMR spectrum of cabergoline solvate Form V.

Form I can be readily prepared according to the present invention starting from crude material by crystallization from a toluene/diethyl ether mixture, through a new solvate form V of cabergoline. The present process for preparing Form I shows advantages with respect to the old one because of its greater reproducibility.

Characterisation

X-ray powder diffraction (XRD), differential scanning calorimetry (DSC), infrared (IR) spectroscopy and solid state ^{13}C-NMR were used to characterise the new form.

X-Ray Powder Diffraction

Powder X-ray diffraction was performed using either a Scintag X1 or X2 Advanced Diffraction System operating under Scintag DMS/NT© Ver 1.30a and 1.36b respectively, and Microsoft Windows NT 4.0™ software. The system used a copper X-ray source maintained at 45 kV and 40 mA to provide CuKα_1 emission of 1.5406 Angstroms and a solid state peltier cooled detector. Beam aperture was controlled using tube divergence and anti-scatter slits of 2 and 4 mm and detector anti-scatter and receiving slits of 0.5 and 0.3 mm width. Data were collected from 2° to 30° two-theta using a step scan of 0.03°/point with a one second/point

counting time. The samples were hand ground using a pestle and mortar and packed into an aluminum sample tray with a 12mm (diam.) x 0.5mm cavity.

DSC

Measurements of differential scanning calorimetry were obtained on a Mettler TA 4000 thermal analysis system. Approximately 8.5 mg samples were accurately weighed into a DSC pan. The pans were hermetically sealed and a pinhole was punched into the pan lid. The use of the pinhole allows for pressure release, but still assures that the thermal reactions proceed under controlled conditions. The samples were introduced into the DSC oven and then heated at a rate of 5°C/min, up to a final temperature of 135°C.

IR Spectroscopy

IR spectra of cabergoline form I and V were obtained on a Perkin Elmer FT-IR spectrophotometer PARAGON 1000. The sample were prepared by KBr powder technique registering the spectra on reflectance.

Solid state ^{13}C-NMR

Solid state ^{13}C-NMR spectra were obtained on a MSL 300 Bruker instrument equipped with solid state facilities and variable temperature magic angle spinning probe. Cross polarisation experiments were performed by a decoupling field of 50 KHz and single pulse magic angle spinning experiments with recycle times ranging from 10 to 100 records.

The x-ray powder diffraction pattern for Form I (Figure 1) shows a crystalline structure with useful distinctive peaks at approximately 9.7, 10.4 and 24.8 deg 2-theta.

The DSC curve of Form I (Figure 2) exhibits a melting endotherm at approximately 100°- 105°C. The integrated melting endotherm has a heat of fusion of approximately 60 J/g.

The IR spectrum of Form I is shown in Figure 3.

The solid state ^{13}C-NMR spectrum of form I is shown in figure 4.

These data indicate that cabergoline Form I is a crystalline polymorph easily distinguishable by XRD and solid state ^{13}C-

NMR techniques. DSC and IR are other two useful techniques to characterize the polymorph. The process of the present invention for producing crystalline cabergoline Form I is characterized by crystallisation from a toluene/diethyl ether mixture. The process comprises dissolving the raw final cabergoline, obtained as an oil through the synthesis described in Eur. J. Med. Chem.,24, 421,(1989), in a suitable amount of a toluene/diethyl ether mixture, preferably about 1:1 mixture. The resultant solution is then cooled at a temperature of from -25° to -9°C, preferably at about -12°C for 17 hours. In these conditions, a toluene solvate is obtained, named Form V, that may be recovered by common procedures, for example by filtration under reduced pressure or by centrifugal filtration, followed by smoothly drying of the resultant solid. The resultant crystals of Form V are then converted into form I upon further drying. The crystals of Form I of cabegoline prepared according to the process of the present invention have preferably a polymorph purity > 95%, more preferably >98%. Toluene solvate form V is also object of the present invention. The x-ray powder diffraction pattern for Form V (Figure 5) shows a crystalline structure.

The DSC curve of solvate Form V (Figure 6) exhibits a melting endotherm at approximately 60°-65°C.

The IR spectrum of solvate Form V is shown in Figure 7.

The solid state ^{13}C-NMR spectrum of form V is shown in figure 8.

These data indicate that cabergoline solvate Form V is easily distinguishable by XRD, DSC and solid state ^{13}C-NMR techniques. IR, combined with another analytical technique, is another method to identify the solvate.

The solvate V of this invention is a true solvate having a fixed composition of about 0.5 toluene moles per mole of cabergoline.

Example 1.

The oil obtained by purification on a chromatographic column after the final step of the synthetic path according to the

preparation described in Eur. J. Med. Chem.,24, 421,(1989) and containing 100 g of pure cabergoline was dissolved in toluene to give 243 g of a cabergoline toluene solution. The solution was introduced into a reactor pre-cooled at -12°C, and 182 g of toluene were added to give a 23.5% w/w cabergoline concentration in this solvent. After cooling again at -12°C, 362 ml of diethyl ether were added. The mixture was cooled again at -12°C and stirred at this temperature for about 17 hours. The obtained precipitate was filtered under vacuum and smoothly dried. The resultant crystal solvate form V was identified by XRD, DSC, IR and NMR, data shown in figures 5-8 respectively.
Yield was about 45%(w/w) on the basis of pure cabergoline initial content.

Example 2.

The crystal solvate form V obtained in example 1 was dried at a temperature of from 40°C under vacuum to 65°C under vacuum. After drying, the resultant crystal form I was identified by XRD, DSC, IR and NMR, data shown in figures 1-4 respectively. Yield was about 40% on the basis of pure cabergoline initial content. The assayed polymorph purity was >98%.

CLAIMS

1. A process for producing cabergoline Form I, which process comprises crystallisation of the desired crystalline form from a toluene/diethyl ether mixture comprising raw cabergoline, followed by recovery and drying of the resulting crystals.

2. A process according to claim 1 in which the crystallisation comprises dissolving raw cabergoline in a toluene/diethyl ether mixture, cooling the resulting solution, collecting the resulting solvate form V of cabergoline having the XRD powder pattern of Figure 5 and converting the solvate into cabergoline Form I by drying.

3. A process according to claim 1 or 2 in which the toluene/ diethyl ether mixture is a 1:1 mixture.

4. A process according to claim 2 or 3 in which the toluene/diethyl ether mixture is cooled to a temperature of from -25° to -9°C.

5. A process according to claim 4, in which the toluene/diethyl ether mixture is cooled to a temperature of about -12°C.

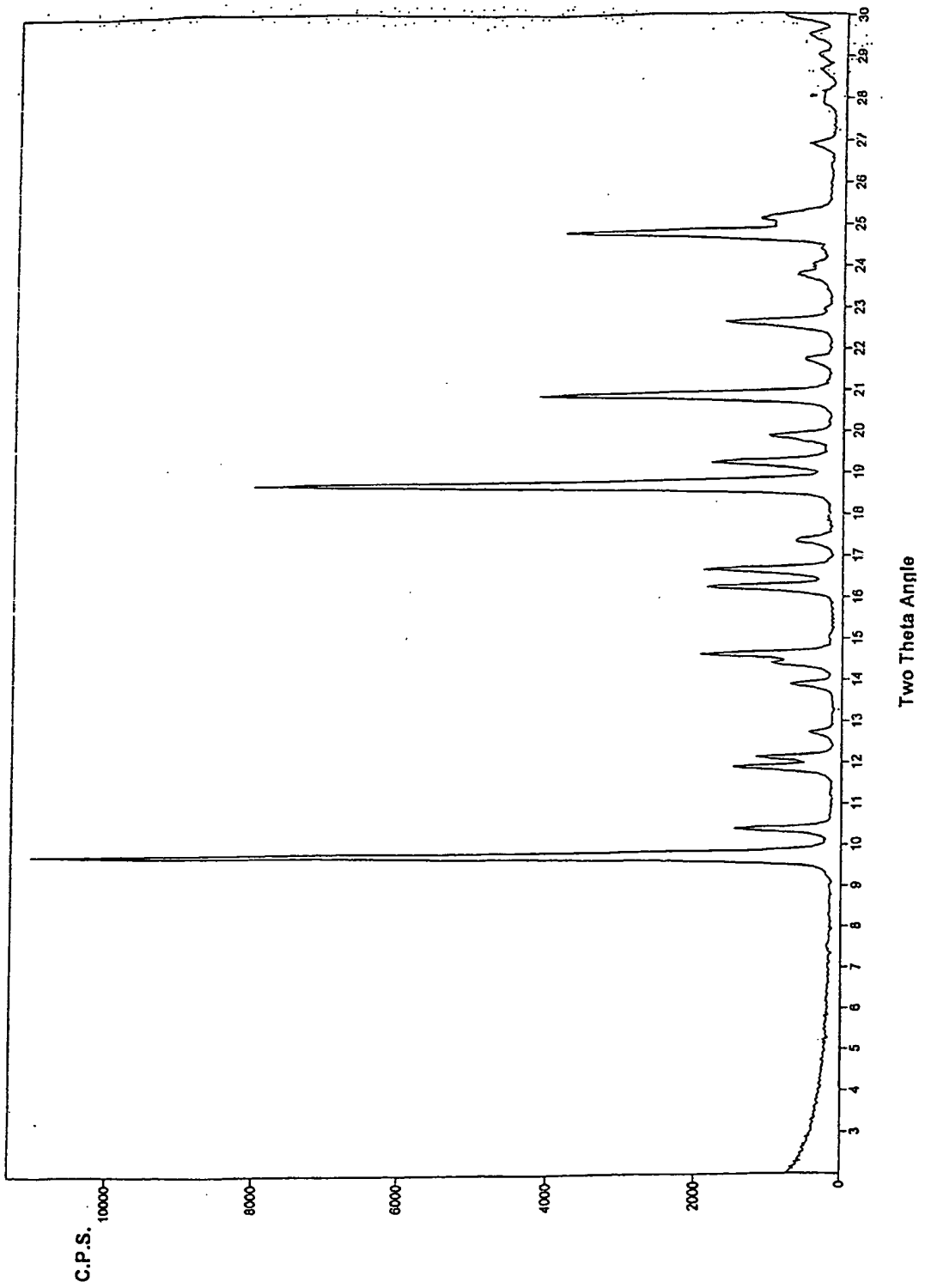
6. Solvate form V of cabergoline having the XRD powder pattern of Figure 5.

7. A process for producing solvate form V of cabergoline as defined in claim 6, which process comprises dissolving raw cabergoline in a toluene/diethyl ether mixture, cooling the resulting solution and collecting the resulting solvate form V of cabergoline.

8. A process according to claim 9 in which the toluene/ diethyl ether mixture is a 1:1 mixture.

9. A process according to claim 7 or 8, in which the toluene/diethyl ether mixture is cooled to a temperature of from -25° to -12°C, and the solvate form V is collected by filtration under reduced pressure or by centrifugal filtration, followed by smoothly drying the resulting solid.

FIG. 1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Two Theta Angle

FIG. 2

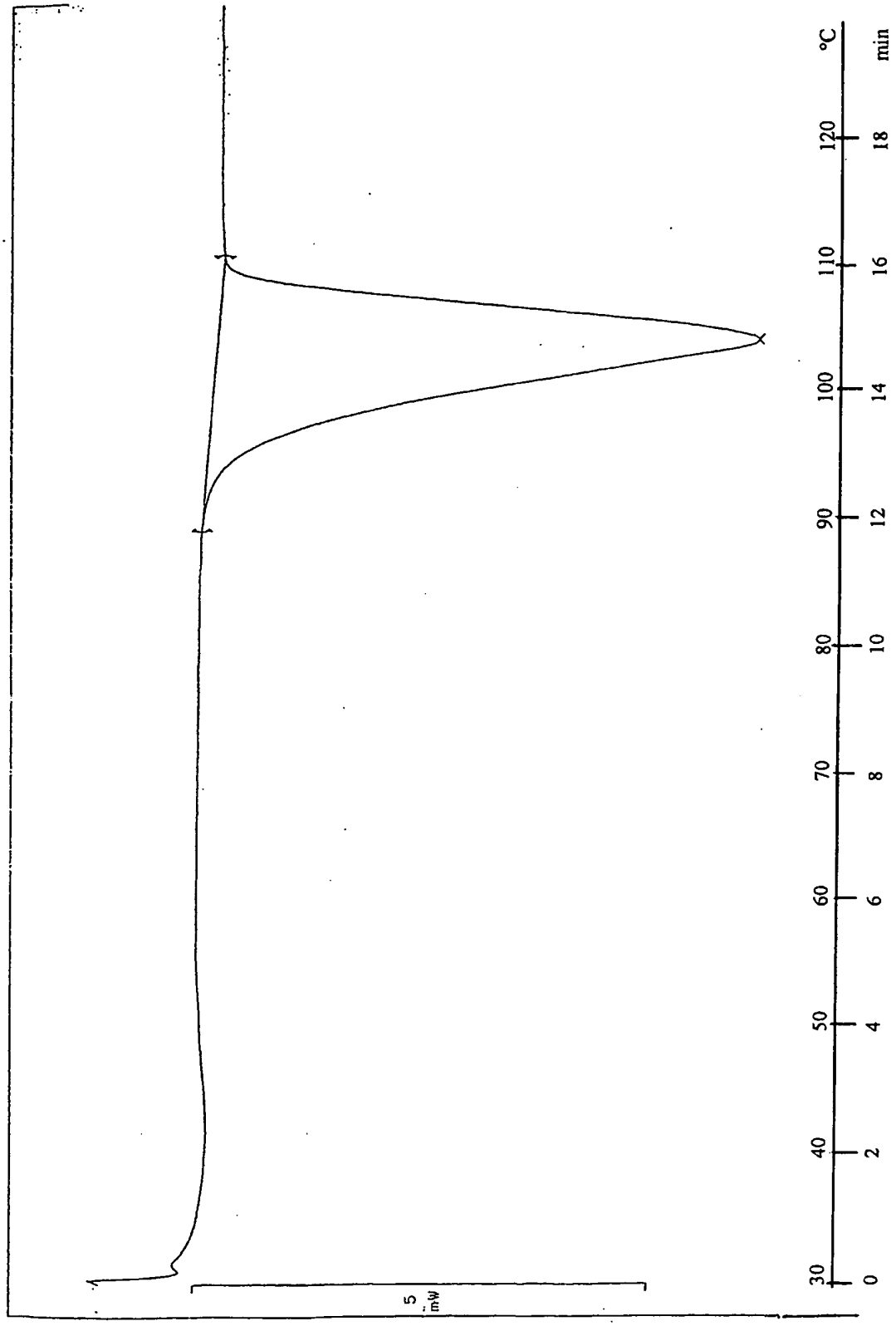
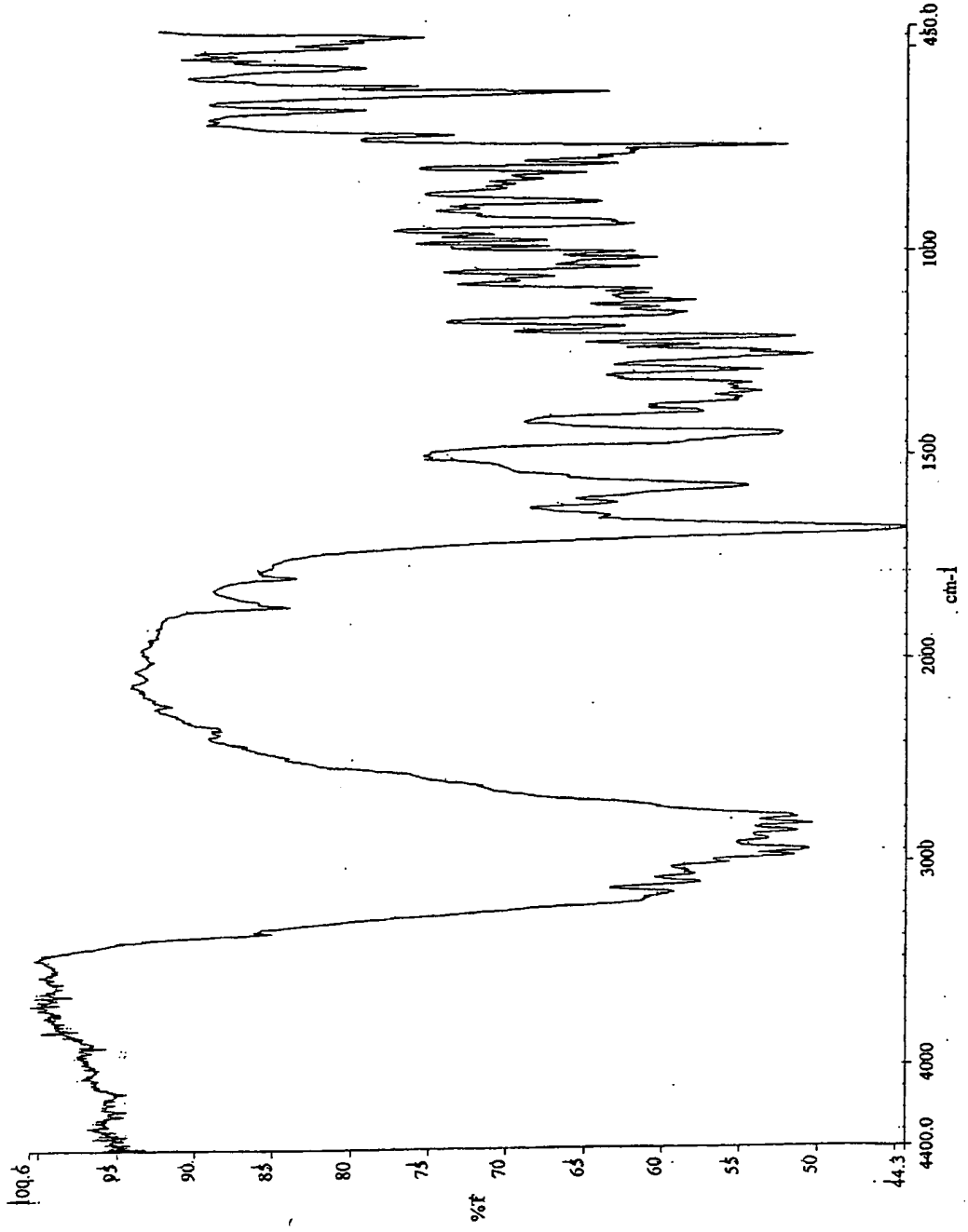


FIG. 3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85
80
75
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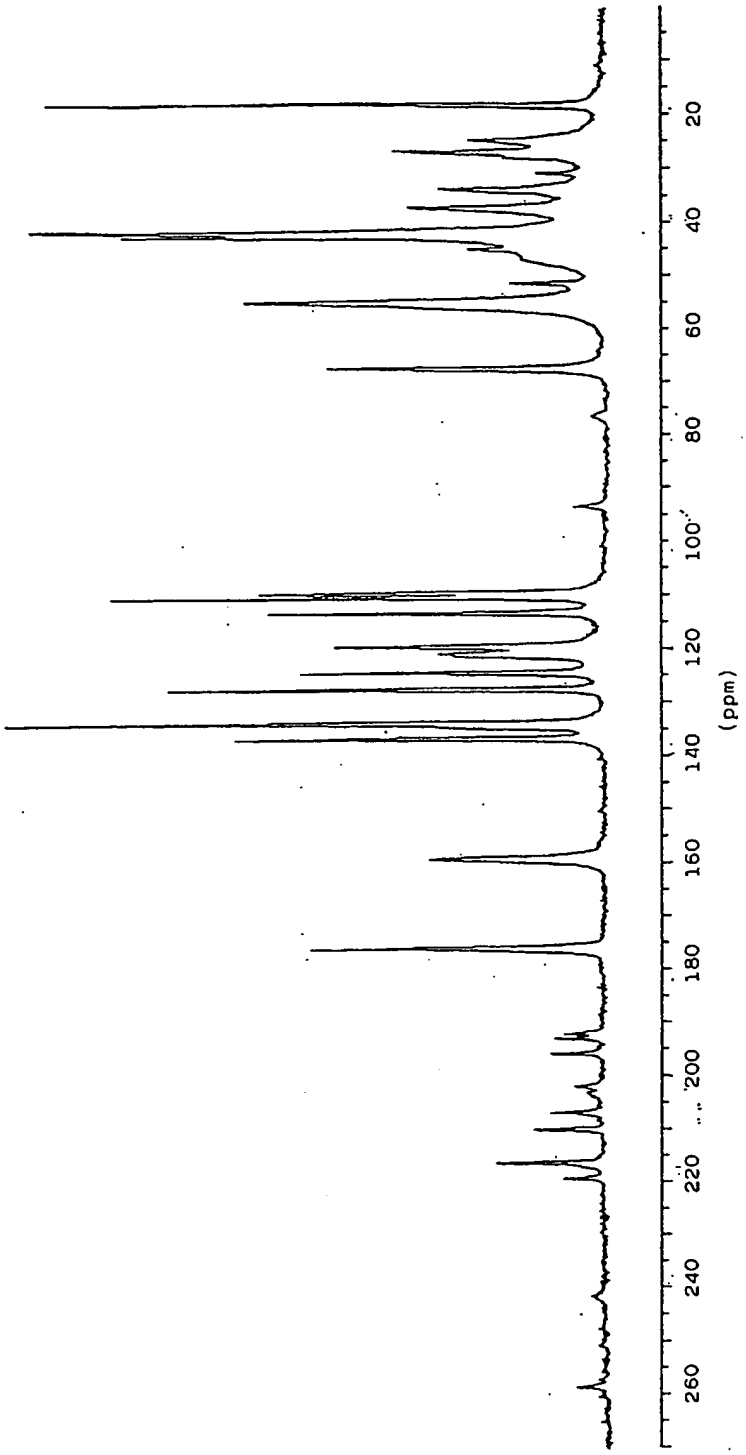
cm-1

FIG. 4



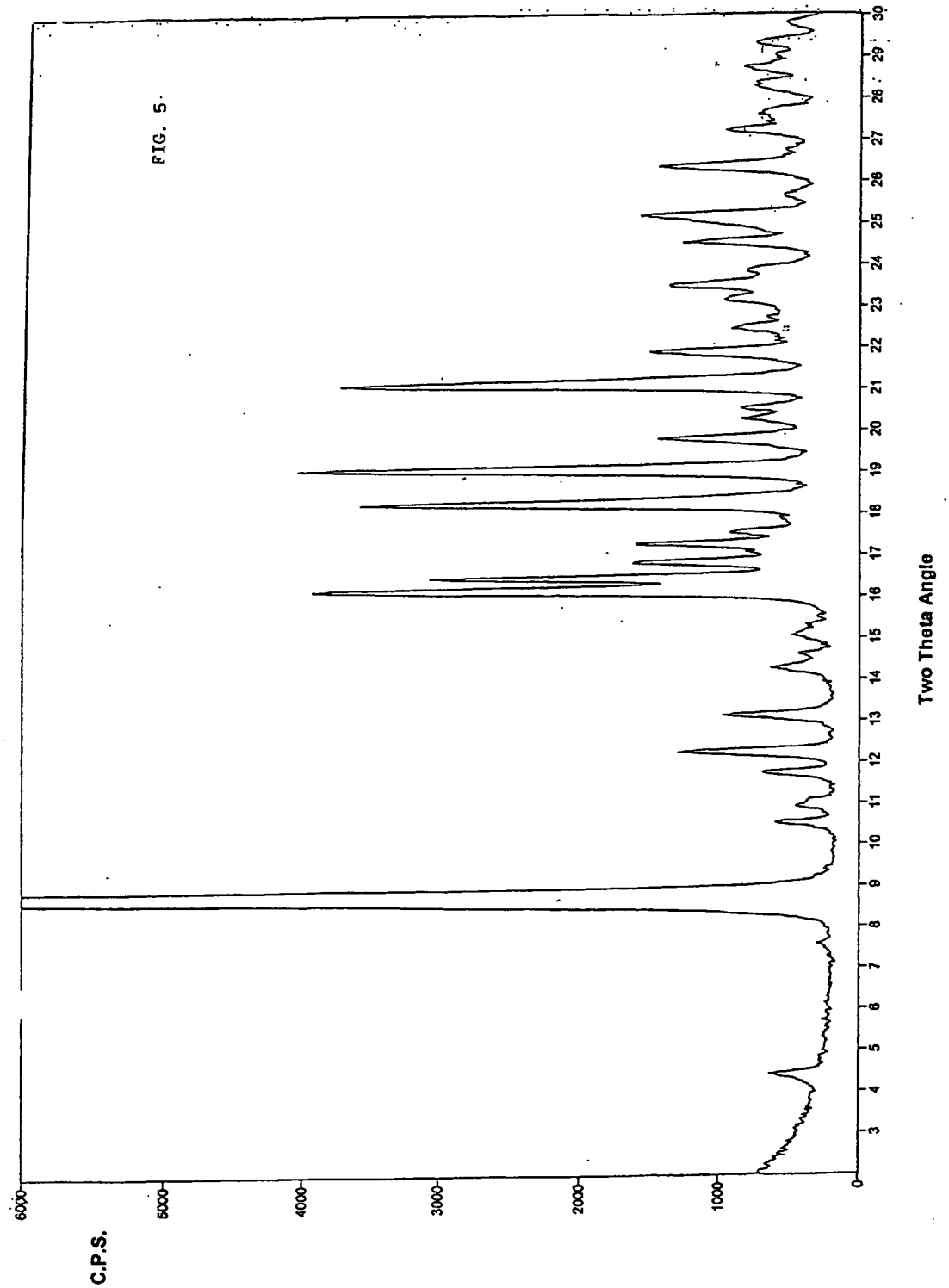


FIG. 5
C.P.S.
6000
5000
4000
3000
2000
1000
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4
5
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Two Theta Angle

FIG. 6

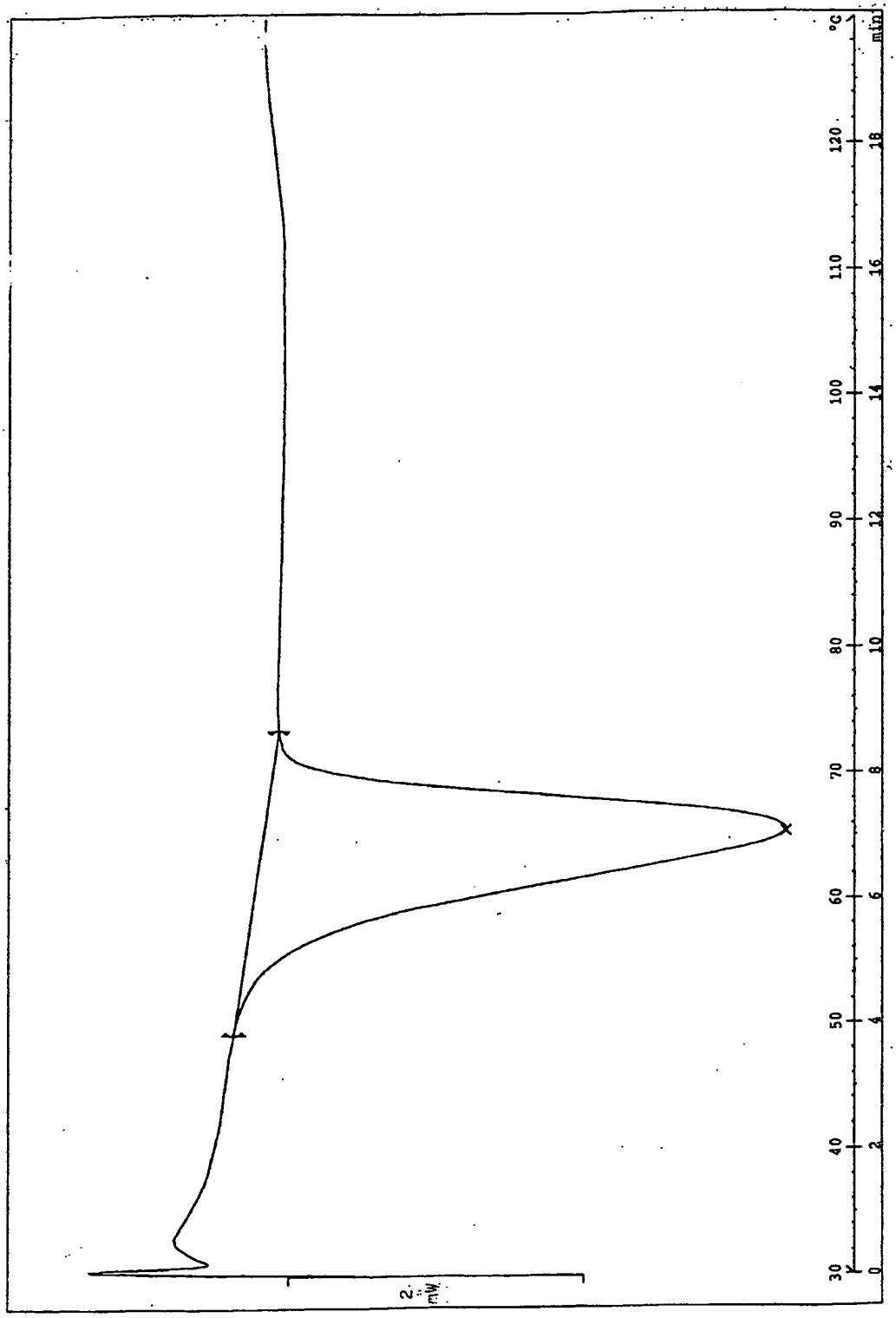
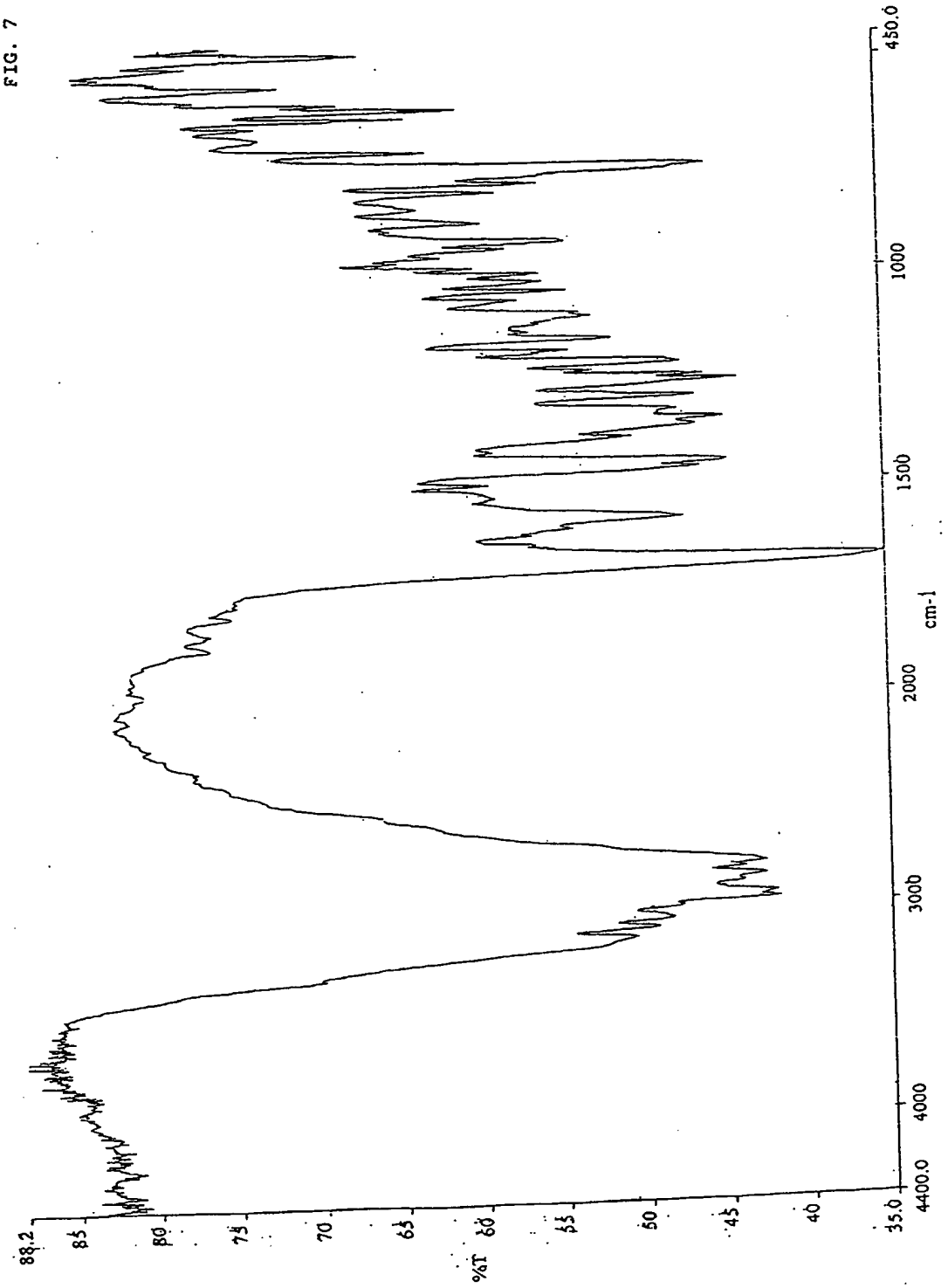


FIG. 7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3000
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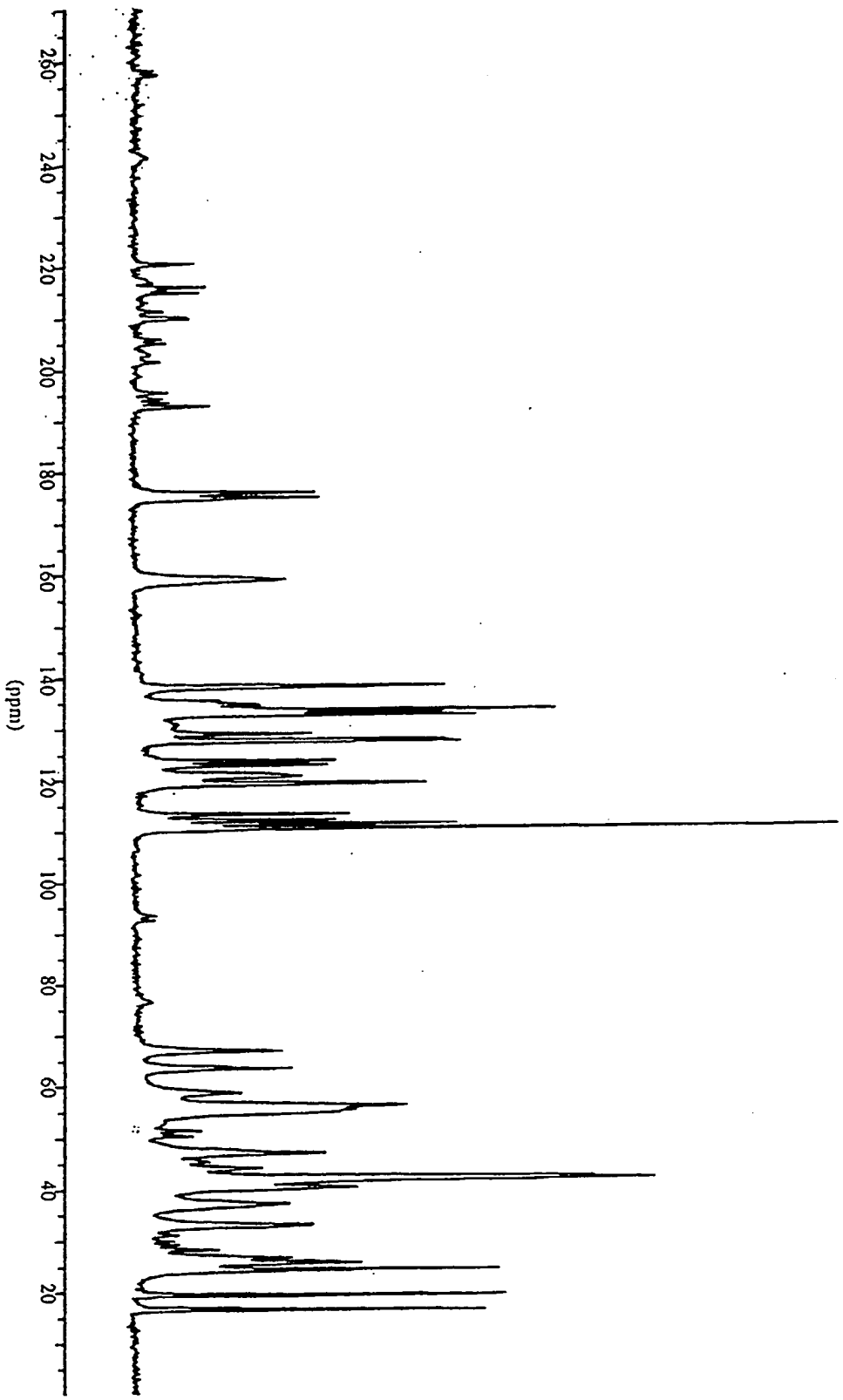

FIG. 8

INTERNATIONAL SEARCH REPORT

In onal Application No
PCT/EP 01/03099

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D457/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

WPI Data, EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	SABATINO P ET AL: "X-RAY CRYSTAL STRUCTURE AND CONFORMATIONAL ANALYSIS OF N-(3-DIMETHYLAMINOPROPYL)-N-(ETHYLAMINOCARBONYL)-6-(2-PROPENYL)ERGOLINE-8BETA-CARBOXAMIDE (CABERGOLINE): COMPARISON WITH BROMOCRIPTINE AND LISURIDE AND A HYPOTHESIS FOR ITS HIGH DOPAMINERGIC ACTIVITY" FARMACO, SOCIETA CHIMICA ITALIANA, PAVIA, IT, vol. 50, no. 3, 1995, pages 175-178, XP001000162 ISSN: 0014-827X cited in the application Page 175, Experimental Section: "crystals of Cabergoline were grown from ethylic ether". --- -/--	1-9

[X] Further documents are listed in the continuation of box C. [X] Patent family members are listed in annex.

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
7 August 2001	17/08/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Weisbrod, T

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Inte ial Application No
P EP 01/03099

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	BRAMBILLA E ET AL: "SYNTHESIS AND NIDATION INHIBITORY ACTIVITY OF A NEW CLASS OF ERGOLINE DERIVATIVES SYNTHESE ET ACTIVITE INHIBITRICE SUR LA NIDATION D'UNE NOUVELLE CLASSE DE DERIVES DE L'ERGOLINE" EUROPEAN JOURNAL OF MEDICINAL CHEMISTRY.CHIMICA THERAPEUTICA, EDITIONS SCIENTIFIQUE ELSEVIER, PARIS, FR, vol. 24, 1989, pages 421-426, XP001005360 ISSN: 0223-5234 cited in the application Page 424, Exp. Protocol for compound IX: "after cryst. from diethyl ether, IX was obtained as a white solid, mp. 102-104 °C".	1-9
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INTERNATIONAL SEARCH REPORT

formation on patent family members

Int al Application No
PC1/EP 01/03099

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